135. (New) An isolated nucleic acid comprising a contiguous portion of SEQ ID NO:7 or its complement, wherein the nucleic acid is 15 to 30 nucleotides.

136. (New) An isolated nucleic acid comprising a contiguous portion of SEQ ID NO:7 or its complement, wherein the nucleic acid is at least 15 nucleotides.

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137. (New) An isolated nucleic acid comprising a nucleotide sequence which encodes a naturally occurring allelic variant of a polypeptide consisting of the amino acid sequence of a Ferroportin1 protein, wherein said nucleic acid hybridizes under high stringency conditions to a nucleic acid consisting of the complement of SEQ ID NO:5.

138. (New) An isolated nucleic acid comprising a contiguous portion of SEQ ID NO:5 or its complement, wherein the nucleic acid is 15 to 30 nucleotides.

139. (New) An isolated nucleic acid comprising a contiguous portion of SEQ ID NO:5 or its complement, wherein the nucleic acid is at least 15 nucleotides.

REMARKS

Claims 1-52, 54-63 and 65-133 are pending in the application. Claims 1-45 and 73-133 have been withdrawn from consideration. Claims 46-52, 54-63 and 65-72 are under examination and have been rejected.

With this Amendment, Claims 63, 66 and 73-133 have been cancelled. Claims 47, 49, 51, 54, 55, 57, 58, 60, 62, 67, and 68 have been amended. Applicant's attorney requests that the examiner kindly reconsider the rejected claims for the reasons set forth below.

Claims 134-139 have been added. For support for Claims 134 and 137, see page 9, lines 7-21. For support for Claims 135 and 138, see page 10, lines 18-26, for example. For support for Claims 136 and 139, see page 2, lines 14-19 and page 12, line 26 to page 13, line 15. No new matter has been added.

Rejection of claims 46-49, 50-52, 54-63, 65-72 under 35 U.S.C. § 112, first paragraph - "scope of enablement"

Claims 46-52, 54-63, and 65-72 have been rejected under 35 U.S.C. § 112, first paragraph, as it is said they are not fully enabled. Claims 47, 49, 51, 54, 55, 57, 58, 60, 62, 67, and 68 have been amended to clarify their meaning.

The claims in question are drawn to isolated nucleic acids comprising nucleotide sequence SEQ ID NO:5 or SEQ ID NO:7, analogous nucleic acids, nucleic acid vectors and cultured cells. The isolated nucleic acids, vectors and cultured cells of the claims can be used in methods for producing a functional polypeptide with iron transport function (Ferroportin1 or a closely related analogous polypeptide), or in methods to characterize nucleic acids encoding Ferroportin1 or Ferroportin1-like polypeptides, or in both categories of methods. The nucleic acids being used for characterization of related nucleic acids would allow elucidation of differences in the nucleotide sequences involved in variations in the function of the iron transport protein Ferroportin1. Each of these uses for the isolated nucleic acids, vectors and host cells has been described in the specification. See for example, page 2, lines 21-25; page 3, lines 15-22; page 13, lines 12-17 and 20-27; page 45, line 21 to page 50, line 27; especially page 47, line 25 to page 48, line 4; and page 49, lines 1-6 regarding portions of SEQ ID NO:5 or SEQ ID NO:7. Using the guidance provided in the specification, one of ordinary skill in the art would be able to make and use the isolated nucleic acids, nucleic acid vectors and cultured cells of the claims, and to carry out the methods for producing functional polypeptides. The Examiner has stated (page 6, lines 7-13 of the Office Action of April 21, 2003):

> In support of a function for the Human iron transporter of SEQ ID NO:6, Applicants have enclosed with the Response of 7 January 2003 (Paper 14) a paper showing a human ferroportin gene that encodes a transporter with iron transport function (Montosi, *et al.*, 2001 J. Clin Invest. 108: 619-623). Data showing that SLC11A3 of the Montosi paper is identical to the gene encoding the human iron transporter of the instant Application and an Information Disclosure Statement documenting the Montosi paper may be persuasive in establishing a function for the claimed nucleotide(s) encoding the human iron transporter peptide.

SLC11A3 as described in Montosi *et al.* is referred to as having GenBank accession No. NM_014585. The entry for GenBank accession No. NM_014585 has undergone several updates since the first deposit of the sequence, and the gene has been reclassified as SLC40A1 rather than SLC11A3. There are three differences between the current sequence for NM_014585 and SEQ

ID NO:5 in the non-coding region, and one silent nucleotide change in the coding region. NM_014585 has an extra C inserted between nucleotides 71 and 72 of SEQ ID NO:5 (cDNA sequence). This is a non-coding base which is 244 bases upstream from the translation initiation site. There are also substitutions at nucleotides 207 and 297 of SEQ ID NO:5 in the upstream non-coding region. A substitution at 967 in the coding region does not change the amino acid sequence. The polypeptides encoded by SEQ ID NO:5 and NM_014585 are completely identical. A comparison of the two polynucleotide sequences using NCBI's "BLAST2" program reveals that the two sequences are identical, except for the differences noted above, and that the complete polypeptide described by Montosi *et al.* is the same as that in SEQ ID NO:6. See Exhibit 1.

For the purposes of using the claimed nucleic acids for diagnostic testing, the three differences in the noncoding region and the silent nucleotide change in the coding region do not make a significant difference. The amino acid sequence of the encoded Ferroportin1 protein is the same in the current entry for GenBank accession no. NM_014585 as in SEQ ID NO:5. In the overlapping regions the two sequences share 2211 out of 2215 possible nucleotides (see BLAST2 of SEQ ID NO:5 and NM_014585; enclosed as Exhibit 1) for 99.82% sequence identity. This 0.18 % difference is on the order of the difference between individuals expected on the basis of allelic variation (where differences in the DNA-sequences result in proteins with identical or nearly identical functions but slightly different molecular structures; see Shastry, B.S. *J. Hum. Genet. 47:* 561-565 (2002), enclosed as Exhibit 2). The isolated nucleic acids comprising SEQ ID NO:5 and SEQ ID NO:7 are clearly the human ferroportin1 gene described in Montosi *et al.* The very minor differences between SEQ ID NO:5 and NM_014585 do not make SEQ ID NO:5 the nucleotide sequence of a different gene.

The Examiner has stated that "specific activities (e.g., unique to the proteins/nucleic acids) of SEQ ID NO:5/6 and the other claimed embodiments are not disclosed." A requirement that utility for nucleic acids be specific has been incorporated into the guidelines for examination for utility. Therefore, an assessment of utility as it applies to the requirement of 35 U.S.C. § 112, first paragraph, to provide a description of how to make and use the invention, is appropriate. The protein encoded by both SEQ ID NO:5 and NM_014585 was shown by Montosi *et al.* to function as an iron transporter (see Montosi *et al.*, 2001, *J. Clin. Invest. 108* at page 621). Utilizing a Xenopus oocyte iron efflux assay as described in the 2000 Nature paper (Donovan, *et al.*, 2000, *Nature 403*: 776-781) and in the specification in Example 3, page 59, lines 14-23, Montosi *et al.*

demonstrated that a mutation that results in the replacement of alanine 77 with aspartate in the human Ferroportin1 resulted in reduced iron export activity in the mutant protein when compared to the normal protein. The assay demonstrated a reduced amount of radioactive iron released (after loading) by oocytes expressing the mutated gene versus oocytes expressing the wild type human ferroportin1 gene. The A77D mutation replaced a small, hydrophobic alanine with a large negatively charged aspartate. This same mutation was found by Montosi *et al.* in all of the patients suffering from hemochromatosis and none of the 200 healthy controls (unaffected family members and other people). This is compelling evidence that the specification has adequately described the ferroportin1 gene (SEQ ID NO:5 and SEQ ID NO:7) encoding the human iron transport protein as described by Montosi *et al.* Since it is identical to the protein of Montosi *et al.*, the encoded polypeptide represented by SEQ ID NO:6 is demonstrated to have a specific function as a human iron transport protein as concluded in the specification. Njajou, *et al.* (*Nature Genetics 28*:213-24 (July 2001); copy provided as reference AX2 of Supplemental Information Disclosure Statement) also describes a single base pair change in the ferroportin1 gene, resulting in an amino acid change which causes hemochromatosis.

The assay reported in Montosi *et al.* presents compelling evidence that the gene with nucleotide sequence SEQ ID NO:5 or SEQ ID NO:7 and its corresponding polypeptide (SEQ ID NO:6) have a specific, substantial and credible utility. One of ordinary skill in the art would be able to make and use the isolated nucleic acids comprising nucleotide sequence SEQ ID NO:5 or SEQ ID NO:7, analogous nucleic acids, nucleic acid vectors and cultured cells, and would be able to perform methods for producing a polypeptide comprising SEQ ID NO:6 and analogous polypeptides, by looking to the complete ferroportin1 gene sequence provided in the specification, in combination with knowledge possessed by a person of ordinary skill in the art. Cloning and manipulating the gene or various fragments thereof for various uses, given the sequence, would be well within the skill of one of ordinary skill in the art. Pages 45-47 of the specification provide instruction on how to identify polymorphisms in an individual's genomic sequence. Following this direction, one skilled in the art could use the isolated nucleic acids of the present invention to characterize and test an individual's nucleic acids for differences which influence Ferroportin1 protein function. Variant nucleic acids, vectors and cultured cells would also be valuable for protein production, for DNA production, and for additional forms of diagnostic testing (as already pointed out in the specification).

Rejection of Claims 55, 58 and 68 under 35 USC §102(b) - "prior art"

Claims 55, 58 and 68 were rejected, as the Examiner said the claims would "encompass all polynucleotide portions found in the earlier reference." Claims 55, 58 and 68 have been amended to more clearly define the invention.

Fujiwara *et al.*, 1995, Accession No. D63209, is a DNA sequence 515 nucleotides long, said to be derived from polyA$^+$ mRNA of human placenta. No further information is given. Accession No. D63209 does not describe an isolated nucleic acid encoding a fusion polypeptide with iron transport activity, a nucleic acid vector of any kind, or a cultured cell of any kind. Fujiwara *et al.* consists of a small fraction of a gene sequence with no direction about its biological relevance or function. It does not provide any direction for an iron transport function, and a person skilled in the art presented with the Fujiwara *et al.* sequence could not recognize this function. The sequence of Fujiwara *et al.* would encode only 22 of the 571 amino acids encoded by the complete ferroportin1 gene. The sequence of Fujiwara *et al.* is missing a C present in SEQ ID NO:5 at position 375, resulting in a frameshift mutation relative to SEQ ID NO:5.

The test for anticipation, interpreting 35 U.S.C. §102, has been set forth numerous times in court decisions. "A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitation of the claim." *EMI Group North America v. Cypress Semiconductor Corp.*, 60 U.S.P.Q.2d 1423, 1429 (Fed. Cir. 2001). "Under U.S.C. §102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987). 35 U.S.C. §102 establishes a novelty standard requiring the single prior art reference to disclose the entire invention in its complete form. "Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." *Gechter v. Davidson*, 43 U.S.P.Q.2d 1030, 1032 (Fed. Cir. 1997).

Fujiwara *et al.* does not anticipate because a person skilled in the art would not be able to make and use the invention as set forth in Claims 55, 58, and 68, based on the teachings of Fujiwara *et al.* Considering the element by element test required for 35 U.S.C. §102, for anticipation of Claims 55, 58, and 68, Fujiwara *et al.* would need to teach how to construct a nucleic acid encoding a fusion polypeptide, a nucleic acid vector and a cultured cell, respectively. Fujiwara *et al.* do not teach a nucleic acid encoding a fusion polypeptide as in Claim 55, nor do they teach the nucleic acid vector as disclosed in Claim 58. Claims 55 and 58 also specifically encompass an isolated nucleic acid, and nucleic acid vector comprising nucleic acid, respectively,

both nucleic acids encoding functional fusion polypeptides not taught by an obscure and incomplete DNA sequence. The iron transport function disclosed by the inventors is not a property taught by Fujiwara *et al.* or inherently in the disclosure of Fujiwara *et al.* Claim 68 is drawn to a cultured cell, an element totally missing from Fujiwara *et al.* Fujiwara *et al.* is lacking elements found in each of Claims 55, 58 and 68. Because these elements are not taught literally or present inherently, there can be no anticipation.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii).

47. (Twice Amended) An isolated nucleic acid having at least 80% nucleotide sequence identity to a nucleic acid encoding a polypeptide comprising the amino acid sequence SEQ ID NO:6, wherein said polypeptide has iron transport activity.

49. (Amended) An isolated nucleic acid comprising a portion of nucleotide sequence SEQ ID NO:5 which encodes a contiguous portion of at least 190 amino acids of SEQ ID NO:6.

51. (Amended) An isolated nucleic acid comprising a nucleotide sequence which encodes a naturally occurring allelic variant of a polypeptide consisting of the amino acid sequence of a Ferroportin1 protein, wherein said nucleic acid [molecule] hybridizes under high stringency conditions to the complement of the sequence SEQ ID NO:5.

54. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding a polypeptide having iron transport activity, wherein said nucleotide sequence shares at least 80% sequence identity with the nucleotide sequence SEQ ID NO:5.

55. (Amended) An isolated nucleic acid encoding a fusion polypeptide having iron transport activity, said nucleic acid molecule comprising a nucleotide sequence encoding all or a portion of an amino acid sequence SEQ ID NO:6, and further comprising a nucleotide sequence encoding a heterologous portion of said fusion polypeptide.

57. (Amended) A nucleic acid vector comprising nucleic acid having at least 80% nucleotide sequence identity to a nucleic acid encoding a polypeptide comprising the amino acid sequence SEQ ID NO:6, wherein said polypeptide has iron transport activity.

58. (Amended) A nucleic acid vector comprising nucleic acid encoding a fusion polypeptide having iron transport activity, said nucleic acid [molecule] comprising a nucleotide sequence

encoding all or a portion of an amino acid sequence SEQ ID NO:6, and further comprising a nucleotide sequence encoding a heterologous portion of said fusion polypeptide.

60. (Amended) A nucleic acid vector comprising nucleic acid having at least 80% nucleotide sequence identity to a nucleic acid encoding a polypeptide comprising the amino acid sequence SEQ ID [NO:5] NO:6, wherein the polypeptide has iron transport activity.

62. (Amended) A nucleic acid vector comprising a nucleic acid with at least 80% nucleotide sequence identity to the coding region of SEQ ID NO:5, wherein said nucleic acid encodes a polypeptide with iron transport activity.

67. (Twice Amended) A cultured cell comprising nucleic acid having at least 80% nucleotide sequence similarity to a nucleic acid encoding a polypeptide comprising the amino acid sequence SEQ ID NO:6, wherein said polypeptide has iron transport activity.

68. (Twice Amended) A cultured cell comprising nucleic acid comprising a [nucleotide sequence] contiguous portion of SEQ ID NO:5 which encodes a contiguous portion of at least about 15 amino acids of SEQ ID NO:6.